

## RESEARCH ARTICLE

# Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE $\epsilon$ 4 carriers

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## Funding information

EU Horizon 2020 Grant: "Healthy minds 0-100 years: Optimising the use of European brain imaging cohorts ('Lifebrain').", Grant/Award Number: 732592; The European Research Council's Starting/Consolidator Grant, Grant/Award Numbers: 283634, 725025, 313440; Norwegian Research Council; The National Association for Public Health's dementia research program, Norway; Medical Student Research Program at the University of Oslo; Partially supported by a Spanish Ministry of Economy and Competitiveness (MINECO), Grant/Award Number: PSI2015-64227-R; Walnuts and Healthy Aging study, Grant/Award Number: NCT01634841; California Walnut Commission, Sacramento, California; German Federal Ministry of Education and Research, Grant/Award

## Abstract

**Introduction:** The apolipoprotein E (APOE)  $\epsilon$ 4 allele is the main genetic risk factor for Alzheimer's disease (AD), accelerated cognitive aging, and hippocampal atrophy, but its influence on the association between hippocampus atrophy and episodic-memory decline in non-demented individuals remains unclear.

**Methods:** We analyzed longitudinal (two to six observations) magnetic resonance imaging (MRI)-derived hippocampal volumes and episodic memory from 748 individuals (55 to 90 years at baseline, 50% female) from the European *Lifebrain* consortium.

**Results:** The change-change association for hippocampal volume and memory was significant only in  $\epsilon$ 4 carriers ( $N = 173$ ,  $r = 0.21$ ,  $P = .007$ ; non-carriers:  $N = 467$ ,  $r = 0.073$ ,  $P = .117$ ). The linear relationship was significantly steeper for the carriers [ $t(629) = 2.4$ ,  $P = .013$ ]. A similar trend toward a stronger change-change relation for carriers was seen in a subsample with more than two assessments.

**Discussion:** These findings provide evidence for a difference in hippocampus-memory association between  $\epsilon$ 4 carriers and non-carriers, thus highlighting how genetic factors

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Number: 16SV5537/16SV5837/16SV5538/  
16SV5536K/01UW0808/01UW0706/01GL1716A/  
BMBF funded Energi consortium, Grant/Award  
Number: 01GQ1421B

modulate the translation of the AD-related pathophysiological cascade into cognitive deficits.

**KEYWORDS**  
apolipoprotein (APOE)  $\epsilon$ 4, hippocampus, longitudinal, memory, MRI

1 | INTRODUCTION

The  $\epsilon$ 4 allele of the apolipoprotein E (APOE) gene is the major genetic risk factor for late-onset Alzheimer's disease (AD).<sup>1–3</sup> Studies show accelerated hippocampal<sup>4</sup> and episodic-memory<sup>5</sup> decline in AD patients with the APOE  $\epsilon$ 4 allele. In a study of Alzheimer's disease (AD) and dementia with Lewy bodies, an association between memory recall scores and hippocampal volume was restricted to APOE  $\epsilon$ 4 carriers.<sup>6</sup> Such a change-change relation provides evidence for correlated changes of hippocampus structure and memory in APOE  $\epsilon$ 4 carriers. The lack of an association in  $\epsilon$ 4 non-carriers was suggested to be due to other factors being more relevant for the hippocampus-memory relation in this group. This suggestion is in line with a model in which genetic variation influences how the AD pathological changes confer greater cognitive impairment in some individuals, that is, those with more risk alleles.<sup>7</sup> As such, this topic pertains to the fundamental clinical and preclinical question of how various pathophysiological brain changes translate into cognitive impairment in different individuals.

In non-demented individuals, the support for a longitudinal hippocampus-episodic memory change-change relation is limited,<sup>8–11</sup> but APOE  $\epsilon$ 4 has been associated with accelerated cognitive aging<sup>12–14</sup> and hippocampal atrophy.<sup>15,16</sup> Thus a differential influence of APOE  $\epsilon$ 4 on brain-cognition associations, reflecting greater phenotype-relevant heterogeneity in non-carriers, might characterize also cognitively normal older adults and preclinical dementia. However, no study to date has comprehensively assessed the longitudinal interrelationships among hippocampus atrophy, episodic-memory decline, and APOE  $\epsilon$ 4 in healthy, non-demented individuals.

Herein, we tested the hypothesis of a difference in longitudinal relations between hippocampal atrophy and linear episodic memory changes between non-demented APOE  $\epsilon$ 4 carriers and non-carriers.

2 | METHODS

2.1 | Lifebrain sample

The sample was derived from the European Lifebrain project ([www.lifebrain.uio.no](http://www.lifebrain.uio.no)). In the present analyses, individuals from six studies within four sites<sup>18–25</sup> were included (Table 1, see also Supplementary material or<sup>26</sup> for the inclusion criteria for each study). Healthy non-demented study participants at least 55 years old at first measurement occasion with both memory and hippocampus measurements available ("baseline" in what follows) and with at least two memory and hippocampus measurements at least 2 years apart were included. For individuals with several follow-up measures available, the first measurement after a minimum of 2 years from baseline was considered as a follow-up. In total, data on longitudinal annual changes in hippocampal volume and episodic memory were available for 748 individuals. Data on change over multiple (ie, more than two) assessments of memory and hippocampus volume involved 214 participants (841 observations) from the Barcelona and Oslo cohorts. For these individuals, the follow-up time was up to 11 years (for descriptive data, see Supplementary Table 1; for number of subjects per number of available measurements, see Supplementary Table 2).

TABLE 1 Sample characteristics

Study	Unique participants	Mean baseline age (range)	Sex (%female /%male)	Mean baseline MMSE (range)/not available	Mean years of education (range)/not available	APOE 4 (carrier/non-carrier/APOE status not available)	Mean follow-up interval (range)
Barcelona/WAHA	40	68.92 (64,76)	68/32	29 (25,30)/0	10.8 (2,18)/0	7/33/0	3.28 (2,5)
Berlin/Base II	166	69.95 (61,80)	40/60	28.5 (22,30)/11	14.2 (7,18)/12	40/125/1	2.54 (2,3)
Oslo/CERAD	87	73.53 (64,90)	55/45	29.2 (25,30)/0	15 (7,23)/13	34/40/13	3.88 (2,6)
Oslo/CVLT	203	67.67 (55,85)	57/43	29 (26,30)/0	15.8 (8,22)/2	30/85/88	3.44 (2,9)
Umeå/Betula	138	64.35 (55,80)	46/54	28.1 (24,30)/0	13.3 (6,26)	34/99/5	4.74 (4,5)
Umeå/ COBRA	114	66.17 (64,68)	46/54	29.3 (27, 30)/0	13.3 (7,25)	28/85/1	5 (5,5)
Total	748	68.08 (55,90)	50/50	28.8 (22,30)/11	14.2 (2, 26)/27	173/467/108	3.76 (2,9)

## 2.2 | Assessments of episodic memory

Each of the participating studies contributed with one or several measures of episodic memory. Table 2 summarizes the tasks used in each study, and Supplementary Figure 1 illustrates the distribution of individual tests at baseline. To define an episodic-memory score for each study, we scaled scores for each individual test by mean and standard deviation of the respective test at study baseline. Then we used the mean of scaled test scores as an episodic memory score at each measurement occasion. Note that scaling was performed by study because of the different scales of tests across data sets, but study was added as a covariate in the analyses.

## 2.3 | Magnetic resonance imaging acquisition and analysis

*Lifebrain* MRI data originated from six different scanners (Table 3), processed with FreeSurfer 6.0 (<https://surfer.nmr.mgh.harvard.edu/>), generating hippocampal and intracranial volume estimates. Because FreeSurfer is almost fully automated, to avoid introducing possible study-specific biases, gross quality control measures were imposed and no manual editing was done. To assess the influence of scanner on hippocampal volume estimates, seven participants were scanned on seven different *Lifebrain* scanners.<sup>26</sup> As reported in,<sup>26</sup> there was a significant main effect of scanner on hippocampal volume ( $F = 4.13 [2.1, 30]$ ,  $P = .046$ ) in this sample. However, the between-participant rank order was almost perfectly retained between scanners. In addition, a mean of pairwise Pearson correlations between bilateral hippocampal volumes measured by different scanners was  $r = 0.98$  (range 0.94 to 1.00).

## 2.4 | Statistical analyses

Analyses were run in R 3.4.4,<sup>27</sup> and the code for the analyses is provided in the Supplementary material.

We considered a linear change of episodic memory and bilateral hippocampus volume. The linear change was estimated for each participant individually as the ordinary least squares slope estimate in the linear regression of memory score (or hippocampus volume) against the participant's age.

Measurements only at two occasions were available for 71% of the subjects in the sample. Therefore, we provide analyses of two estimates of linear change.

First, to be consistent in the number of measurements used in estimation, we estimated the linear change using two measurements for each participant. Note that in this case, the ordinary least squares slope is equal to the annual change, calculated as

$$(X_{\text{follow-up},i} - X_{\text{baseline},i}) / (\text{follow-up age}_i - \text{baseline age}_i),$$

where  $X_{\text{baseline},i}$  is the memory score or hippocampus volume at the baseline for subject  $i$ , and  $X_{\text{follow-up},i}$  is the value of the respective mea-

### RESEARCH IN CONTEXT

- 1. Systematic review:** Previous studies have shown that the apolipoprotein E (APOE)  $\epsilon 4$  allele confers elevated risk for Alzheimer's disease (AD), accelerated cognitive aging, and hippocampal atrophy. This work is properly cited. The influence of APOE  $\epsilon 4$  on the association between hippocampal atrophy and episodic-memory decline in non-demented individuals remains unclear.
- 2. Interpretation:** Our finding of a differential longitudinal change-change association for hippocampus and memory in APOE  $\epsilon 4$  carriers compared to non-carriers supports a model in which genetic factors modulate the translation of the AD-related pathophysiological cascade into memory deficits.
- 3. Future directions:** We propose validation of our findings in forthcoming multi-wave longitudinal studies of brain-cognition relations, combined with appropriate statistical methods for analyzing longitudinal data. Future investigations can specify the exact mechanisms that foster differences in hippocampus-memory relations between APOE  $\epsilon 4$  carriers and non-carriers.

sure at the follow-up. We refer to such estimates of linear changes using two measurements as "annual changes" further in the text.

Second, a subsample of participants from the Oslo and Barcelona cohorts had more than two repeated measurements available (see Supplementary Table 2 for a number of participants by the amount of repeated measures). Therefore, in the second analysis, for these subjects, the second measure of the linear change was defined as the ordinary least squares slope estimated using all available repeated observations. In what follows, we refer to such estimators of linear changes as "slopes."

For description of the relation between the longitudinal observations and age, we used the linear mixed-effect model with a linear term for age and a random intercept for each subject and generalized additive mixed model (GAMM,<sup>28</sup> using *gamm4* R package<sup>29</sup>) with a semi-parametric term for age and a random intercept for each subject.<sup>26</sup> Akaike information criterion, bayesian information criterion, and likelihood ratio tests were used to compare the GAMM and the linear mixed effect model fit to the observed data (see Supplementary materials for details on fitting and R code).

Next, we used partial correlations adjusted for age at baseline, sex, and study to test the significance of hippocampus-memory change-change associations. Study was included as a covariate in the analyses to adjust for the differences in cognitive assessments between the included studies. In addition, since for five of six included studies magnetic resonance imaging (MRI) data were obtained with the same scanner within a study, adjustment for study also captures possible differences in MRI-derived measures due to scanner differences.

**TABLE 2** Memory assessments

Study	Episodic memory tasks	Source for test description/dataset
Barcelona/WAHA	Rey Auditory Verbal Learning total score, Rey Auditory Verbal Learning Test delayed recall, Rey Complex Figure Test	Rajaram et al., 2017 <sup>18</sup> Vaqué-Alcázar et al., 2020 <sup>25</sup>
Berlin/Base II	Verbal Learning and Memory Test (combined immediate and delayed recall), Scene Encoding task (2.5 h delayed recall), Face-Profession task (3 min delayed recall), Object Location task (immediate recall)	Bertram et al., 2014 <sup>19</sup> Gerstorff et al., 2016 <sup>50</sup>
Oslo/CERAD	Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-min delayed recall task	Fjell et al., 2018 <sup>20</sup>
Oslo/CVLT	California learning Verbal test, California learning Verbal test 5-min free recall, California learning Verbal test 30 min free recall	Langnes et al., 2020 <sup>23</sup>
Umeå/Betula	Immediate recall of sentences, Delayed cued recall of words, Immediate recall of words	Nilsson et al., 1997 <sup>21</sup>
Umeå/COBRA	Word recall, Number recall, Object-position recall (all immediate recall)	Nevalainen et al., 2015 <sup>22</sup>

Additional adjustment for the two scanners used in Oslo cohort did not change our main conclusion of differential memory-hippocampus change-change relation between carriers and non-carriers.

Confidence intervals (CIs) for partial correlations were calculated using the Fisher z-transformation and the 5% significance level.

To compare the relationship between hippocampus and episodic memory changes for APOE  $\epsilon 4$  carriers and non-carriers, we ran linear regression of memory changes on hippocampus changes, age, study, sex, an indicator of being an APOE  $\epsilon 4$  carrier, and the interaction term between hippocampus change, and the indicator of being an APOE  $\epsilon 4$  carrier. We used the significance of an interaction term in the linear regression to test if the relationship between hippocampus and episodic memory linear changes in APOE  $\epsilon 4$  carriers is significantly different from the relationship in non-carriers.

## 2.5 | APOE $\epsilon 4$ status

APOE allele  $\epsilon 4$  carriership was defined as APOE alleles  $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ , or  $\epsilon 4/\epsilon 4$ . For details on genotyping methods, see the study-specific details.<sup>18–25</sup>

**TABLE 3** MRI acquisition parameters

Study	Scanner	Tesla	Sequence parameters
Barcelona/WAHA	Tim Trio Siemens	3.0	TR: 2300 ms, TE: 2.98 ms, TI: 900 ms, flip angle: 9°, slice thickness 1 mm, FoV 256 × 256 mm, 240 slices
Berlin/Base II	Tim Trio Siemens	3.0	TR: 2500 ms, TE: 4.77 ms, TI: 1100 ms, flip angle: 7°, slice thickness: 1 mm, FoV 256 × 256 mm, 176 slices
Oslo/CERAD	Avanto Siemens	1.5	TR: 2400 ms, TE: 3.79 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240 × 240 mm, 160 slices
Oslo/CVLT	Avanto Siemens	1.5	TR: 2400 ms, TE: 3.61 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240 × 240 mm, 160 slices, iPat = 2
	Skyra Siemens	3.0	TR: 2300 ms, TE: 2.98 ms, TI: 850 ms, flip angle: 8°, slice thickness: 1 mm, FoV: 256 × 256 mm, 176 slices
Umeå/Betula	Discovery GE	3.0	TR: 8.2 ms, TE: 3.2 ms, TI: 450 ms, flip angle: 12°, slice thickness: 1 mm, FoV 250 × 250 mm, 176 slices
Umeå/COBRA	Discovery GE	3.0	TR: 8.2 ms, TE: 3.2ms, TI: 450 ms, flip angle: 12°, slice thickness: 1mm, FoV 250 × 250 mm, 176 slices.

FoV, field of view; iPat, in-plane acceleration; TE, echo time; TI, inversion time; TR, repetition time.

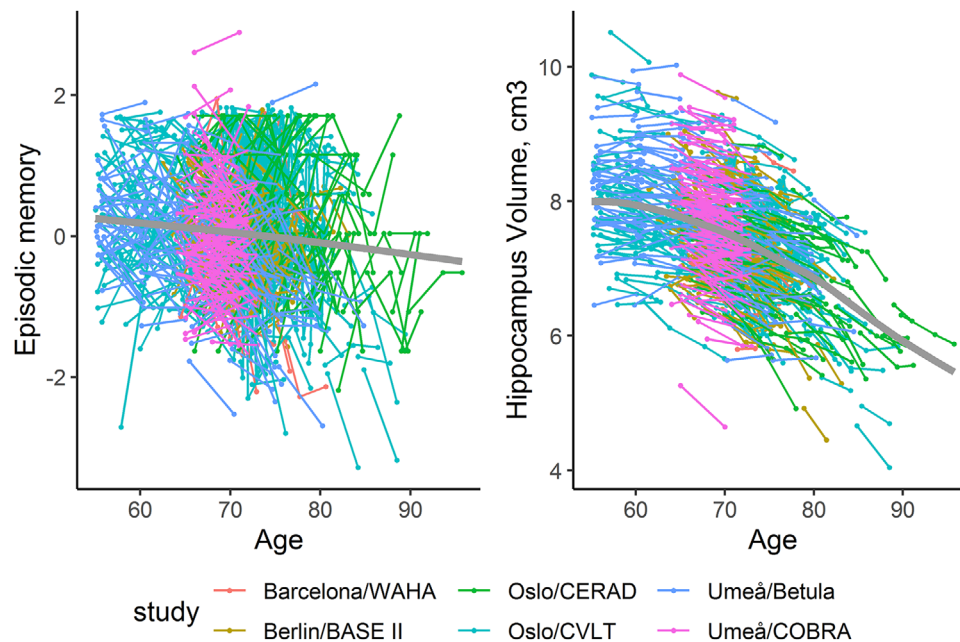
## 2.6 | Data availability

The data supporting the results of the current study may be made available on reasonable request, given appropriate ethical and data protection approvals. Requests for data included in the analyses can be submitted to the relevant principal investigators of each study.

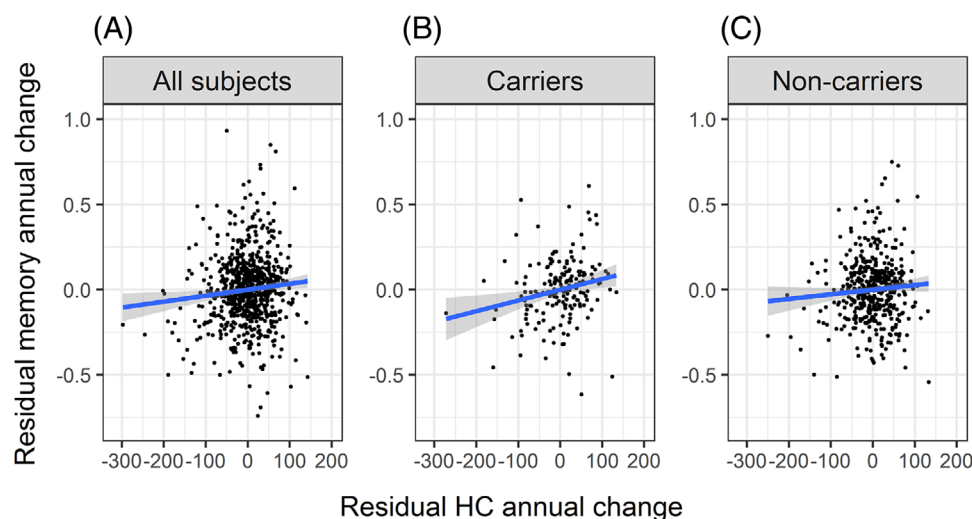
## 3 | RESULTS

### 3.1 | Overall results

Figure 1 shows that there was a general pattern of decline with increasing age for episodic-memory performance as well as for hippocampus volume, with marked individual differences (see also



**FIGURE 1** Individual trajectories for memory and hippocampal change (based on all longitudinal observations). The bold gray line indicates mean change, estimated using a generalized additive mixed model.<sup>28</sup> See Supplementary material for details



**FIGURE 2** Scatterplots of the residuals from the linear regression of hippocampus annual change and episodic memory annual change on baseline age, sex, and study. Blue line—linear regression fit to the data on the scatterplots, gray area represents confidence interval. (A) Scatterplot for all subjects in the sample. (B) Scatterplot for *APOE*  $\epsilon 4$  carriers. (C) Scatterplot for non-carriers of *APOE*  $\epsilon 4$ . For B and C, the respective subsamples were used in calculation of the residuals

Supplementary Table 3). Semiparametric GAMMs<sup>28</sup> fit to the data suggested a significant relation of age to both hippocampus and memory, and a non-linear trend for hippocampus volume (see Supplementary material for details and additional Supplementary Figure 2 for the relation of baseline measures and annual changes to baseline age).

In the total sample ( $N = 748$ ), we found a statistically significant association between linear changes in hippocampus and memory

estimated using two observations for each subject (see Figure 2A); partial correlation between the annual changes, adjusted for baseline age, sex, and study is  $r = 0.093$ ,  $P = .011$ , 95% CI (0.02, 0.16). For the subsample with multiple assessments ( $N = 214$ ), the annual change-change association was  $r = 0.144$ ,  $P = .037$ , CI (0.01, 0.27). When linear changes were estimated by slopes using all available longitudinal observations, the association of linear changes was estimated at  $r = 0.219$ ,  $P = .001$ , CI (0.09, 0.34).



**TABLE 4** Descriptive statistics for APOE  $\epsilon 4$  carriers and non-carriers

APOE $\epsilon 4$ status	N	Mean baseline age (range)	% Female /male	Mean education (range)	Mean follow-up interval (range)	Mean memory, baseline (range)	Mean memory, follow-up (range)	Mean memory annual change (range)	Mean hippocampus volume, baseline	Mean hippocampus volume, follow-up	Mean hippocampus annual change (range)
Carriers	173	68.44 (55, 90)	51/49	14.3 (2, 26)	3.86 (2, 6)	-0.003 (-2, 2)	0 (-3, 2)	0.003 (-1, 1)	7498 (5635, 9887)	7270 (5291, 9548)	-65.11 (-379, 85)
Non-carriers	467	68.08 (55, 88)	51/49	13.9 (4, 26)	3.77 (2, 6)	0.006 (-3, 3)	0.05 (-3, 3)	0.027 (0, 1)	7600 (4922, 9943)	7430 (4450, 10026)	-48.55 (-299, 72)
Group difference		t = 0.7, df = 291, p-v. = 0.49	$\chi^2 = 0.0$ , df = 1, p-val. = 1	t = 1.3, df = 318, p-v. = 0.19	t = 0.9, df = 321, p-v. = 0.37	t = -0.14, df = 318, p-v. = 0.9	t = -0.71, df = 318, p-v. = 0.48	t = -1.34, df = 333, p-v. = 0.18	t = -1.42, df = 296, p-v. = 0.16	t = -2.1, df = 289, p-v. = 0.04	t = -2.74, df = 250, p-v. = 0.007

### 3.2 | Influence of APOE $\epsilon 4$ on hippocampus-memory annual-change relations

Of 640 individuals with APOE genotyping available (Table 4), 27% were considered as carriers. This proportion varied between 17.5% and 46% across the included studies (Table 1). When stratifying the sample into APOE  $\epsilon 4$  carriers (N = 173) and non-carriers (N = 467), the baseline age, sex, and education distributions were similar between subgroups (Table 4). In addition, the mean follow-up time, memory performances at baseline and follow-up, and hippocampus volume at baseline were comparable. The only significant group difference was observed at follow-up, with a significantly smaller hippocampus volume for APOE  $\epsilon 4$  carriers compared to non-carriers (Table 4).

Consistent with our main prediction, the association between annual changes in hippocampus volume and memory (both adjusted for baseline age, sex, and study) was significant for carriers (Figure 2B;  $r = 0.21$ ,  $P = .007$ , CI (0.06, 0.35)) but not for non-carriers (Figure 2C;  $r = 0.073$ ,  $P = .117$ , CI (-0.02, 0.16)). Hippocampus atrophy explained about 4% of the heterogeneity in episodic memory decline for carriers not accounted for by age, sex, or study (partial  $R^2 = 0.044$ ), but <1% for non-carriers (partial  $R^2 = 0.005$ ). The linear relationship between memory and hippocampal annual change was significantly steeper for APOE  $\epsilon 4$  carriers compared to non-carriers (the parameter for the interaction term was estimated as  $b = 0.0006$ ,  $t = 2.4$ ,  $df = 629$ ,  $P = .013$ , two-sided).

### 3.3 | Influence of APOE $\epsilon 4$ on hippocampus-memory slope relations

For the slope calculations, APOE data were available for 172 of the 214 participants with multiple (>2) assessments. The hippocampus-memory slope relationship was  $r = 0.36$  for 51 carriers (adjusted for baseline age, sex, study,  $P = .013$ , CI (0.09, 0.59)), and  $r = 0.22$  for 121 non-carriers ( $P = .018$ , CI (0.04, 0.38)). The hippocampus slope explained 13% of the heterogeneity in episodic memory decline not accounted for by age, sex, or study for carriers ( $R^2 = 0.13$ ), and 5% for

non-carriers ( $R^2 = 0.05$ ). The relationship between memory and hippocampal slopes was again steeper for carriers than non-carriers, but the difference was not significant (the parameter for the interaction term was estimated as  $b = 0.0005$ ,  $t = 0.893$ ,  $df = 164$ ,  $P = .37$ , two-sided;  $z = 0.86$ ,  $P = .2$ , one-sided). The effect size difference was almost identical to the one found in the annual change relations, but the sample size was smaller in this analyses of individuals with multiple assessments.

## 4 | DISCUSSION

The pooled results across the participating *Lifebrain* sites confirmed a relation of increasing age with hippocampus volume as well as episodic-memory performance, along with marked individual differences. We found that age-related longitudinal decline in episodic memory had a weak but significant positive relation to hippocampus atrophy in the total sample, comprising 748 non-demented individuals. When the sample was stratified into APOE  $\epsilon 4$  carriers and non-carriers, the annual change-change association was significant for carriers only, and the linear relation was significantly steeper for carriers compared to non-carriers.

The finding of a robust hippocampus-episodic memory change-change relationship for non-demented APOE  $\epsilon 4$  carriers extends observations in previous studies of patients with dementia.<sup>6,30</sup> The results from a study of aged APOE  $\epsilon 4$  knock-in mice might offer a potential mechanism for the observed differential structure-function relation.<sup>31</sup> Structurally, APOE  $\epsilon 4$  will augment loss of  $\gamma$ -aminobutyric acid (GABA)ergic interneurons in the hippocampal dentate gyrus, which functionally will disrupt slow gamma oscillations during hippocampal sharp-wave ripples and thereby contribute to impaired learning and memory. By this view, with the caveat that our MRI data remain silent about neuron-type and subfield-specific changes, APOE  $\epsilon 4$  could be a common mechanism for hippocampus structure and hippocampus-dependent functions such as episodic memory, which translates into a hippocampus-episodic memory change-change relation for APOE  $\epsilon 4$  carriers. We caution that the group difference in relationship was

modest in size, so the underlying mechanisms might not be APOE-genotype specific but rather amplified in  $\epsilon 4$  carriers. Additional factors could also contribute to this selective effect, including breakdown of the blood-brain barrier in the hippocampus, which in a recent paper predicted future cognitive decline in APOE  $\epsilon 4$  carriers but not in non-carriers.<sup>32</sup>

The weaker structure-function relationship in non-carriers is likely driven by substantial phenotype-relevant heterogeneity. That is, although hippocampus atrophy to some degree may contribute to memory decline in many older individuals, it is likely that other neurobiological changes can be more influential for certain individuals for whom hippocampus atrophy instead can be quite modest. This interpretation resonates with previous multi-factor frameworks of cognitive aging,<sup>33,34</sup> and calls for multivariate analytic approaches that can handle sample heterogeneity in the brain-behavior mapping.<sup>35,36</sup> For example, Lövdén et al.<sup>35</sup> applied latent-profile analysis to dopamine D2 measures from cortex, hippocampus, and the striatum, and to cognitive data from measures of episodic memory, working memory, and perceptual speed. For the majority of the sample, greater receptor availability was associated with better cognition. However, for a subgroup of individuals, high striatal dopamine related to poor working-memory performance. Such sample heterogeneity reduces the strength of overall structure-function relations.

Relatedly, although hippocampus/brain maintenance is the strongest predictor of preserved episodic memory in aging,<sup>37,38</sup> factors like reserve and compensation might enable relatively intact performance possible despite marked brain changes.<sup>39,40</sup> By this view, some individuals with hippocampus atrophy can attain relatively good memory performance by means of effectively recruiting extrahippocampal brain networks. In non-demented aging, elevated hippocampal resting-state functional connectivity has been demonstrated,<sup>41,42</sup> and the older individuals with the highest hippocampal resting-state connectivity had less extensive hippocampus-cortical connectivity during memory encoding.<sup>41</sup> Elevated hippocampal resting-state functional connectivity has also been observed in  $\epsilon 4$  carriers,<sup>43</sup> which thus could reduce the effectiveness of hippocampus-cortical network interactions during cognitive tasks and weaken compensatory processes. Conversely, based on more intact hippocampus-cortical connectivity, APOE  $\epsilon 4$  non-carriers might be more apt at engaging in compensatory processes, which then would contribute toward blurring the hippocampus-memory relation in non-carriers.

The generally stronger change-change associations from slope estimations based on multiple measures over longer period of time, compared with two-time point change estimates, is predicted by past measurement theoretical work.<sup>44</sup> With the accumulation of multi-wave longitudinal studies of brain-cognition relations, combined with appropriate statistical methods for analyzing longitudinal data,<sup>44,45</sup> future analyses will likely reveal stronger change-change relations than in the present two-wave analyses ( $r = 0.093$ ) and in past cross-sectional meta-analyses ( $r = 0.097$ ;<sup>46</sup>). Critically, future change-change relations are still expected to be higher for  $\epsilon 4$  carriers, as indicated by the coherent APOE patterns for annual change as well as slope in this study.

To obtain a reasonable sample size and by inference a sample representative of a wider population, we pooled data across multiple sites in the *Lifebrain* consortium. Similar approaches have been used elsewhere,<sup>47,48</sup> but we acknowledge that the use of different scanners and memory tasks is a limitation of the study that could have impacted the strength and consistency of the observed associations. However, we see no reason that this factor should have affected carriers and non-carriers in different ways. Another limitation is that different procedures were used to assess the clinical status of the participants across sites. We therefore caution that our classification of participants as non-demented should be regarded as tentative. Still, the average Mini-Mental State Exam (MMSE) score at baseline across the entire sample of 748 individuals was close to 29, and in the five studies where MMSE data were available at follow-up only two individuals had a score below 24, which taken together is indicative that the sample as a whole remained non-demented at follow-up. Moreover, we note that many of the participants have or will be followed-up yet again within the specific sites. We note that the bigger change in hippocampus volume in  $\epsilon 4$  carriers could have influenced the chance to observe correlations with memory change, but we view the larger negative change among carriers as part of the phenomenon under study. Finally, the *Lifebrain* database does not include measures of amyloid beta ( $A\beta$ ) or tau, which prevented us from addressing possible mechanistic roles of  $A\beta$  and tau<sup>6</sup> for the difference in hippocampus-memory relation between  $\epsilon 4$  carriers and non-carriers, and the sample was biased toward older age, which prevented us from evaluating whether the observed associations were age invariant.

## 5 | CONCLUSION

In conclusion, a fundamental clinical and preclinical question concerns how various pathophysiological brain changes, such as hippocampal atrophy, translate into cognitive impairment in different individuals. The present findings provide support for the hypothesis that carriage of vital genetic risk alleles increases the risk for cognitive impairment.<sup>7</sup> With the emerging trend of large-scale databases and advances in machine learning,<sup>49</sup> we foresee that future studies will allow better characterization of brain-behavior relations at the individual level that will constitute an important step toward precision medicine.

## ACKNOWLEDGMENTS

The *Lifebrain* project is funded by the EU Horizon 2020 Grant: "Healthy minds 0-100 years: Optimising the use of European brain imaging cohorts ('Lifebrain')." Grant agreement number: 732592 (*Lifebrain*). Call: Societal challenges: Health, demographic change and well-being. In addition, the different sub-studies are supported by different sources: Center for Lifespan Changes in Brain and Cognition: The European Research Council's Starting/Consolidator Grant schemes under grant agreements 283634, 725025 (to A.M.F.) and 313440 (to K.B.W.), as well as the [Norwegian Research Council](#) (to A.M.F., K.B.W.), The National Association for Public Health's dementia research program, Norway (to A.M.F.) and the Medical

Student Research Program at the University of Oslo. Betula: a scholar grant from the Knut and Alice Wallenberg (KAW) foundation to L.N. Barcelona: Partially supported by a Spanish Ministry of Economy and Competitiveness (MINECO) grant to D-BF [grant number PSI2015-64227-R (AEI/FEDER, UE)]; by the Walnuts and Healthy Aging study [<http://www.clinicaltrials.gov>; grant NCT01634841] funded by the California Walnut Commission, Sacramento, California. BASE-II has been supported by the German Federal Ministry of Education and Research [grant numbers 16SV5537/16SV5837/16SV5538/16SV5536K/01UW0808/01UW0706/01GL1716A/01GL1716B] and is also part of the BMBF funded Energi consortium [01GQ1421B].

## CONFLICT OF INTEREST

None reported.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Gorbach T, Pudas S, Bartres-Faz D, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE ε4 carriers. *Alzheimer's Dement*. 2020;12:e12110. <https://doi.org/10.1002/dad2.12110>